

PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)





Applicant's or agent's file reference 2002.732_WO	FOR FURTHER ACTION See Notification of Transmittal of International Preliminary Examination Report (Form PCT/PEA/416)	
International application No. PCT/EP 03/50188	International filing date (day/month/year) 22.05.2003	Priority date (day/month/year) 30.05.2002
International Patent Classification (IPC) or both national classification and IPC A61P15/00		
Applicant AKZO NOBEL N.V.		

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.
2. This REPORT consists of a total of 10 sheets, including this cover sheet.
 - ☐ This report is also accompanied by ANNEXES, i.e. sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

These annexes consist of a total of sheets.

3. This report contains indications relating to the following items:
 - I ☒ Basis of the opinion
 - II ☐ Priority
 - III ☒ Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
 - IV ☐ Lack of unity of invention
 - V ☒ Reasoned statement under Rule 66.2(a)(ii) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
 - VI ☐ Certain documents cited
 - VII ☐ Certain defects in the international application
 - VIII ☐ Certain observations on the international application

Date of submission of the demand 17.10.2003	Date of completion of this report 13.09.2004
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**INTERNATIONAL PRELIMINARY
EXAMINATION REPORT**

International application No. **PCT/EP 03/50188**

I. Basis of the report

1. With regard to the **elements** of the international application (*Replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report since they do not contain amendments (Rules 70.16 and 70.17):*

Description, Pages

1-14 as originally filed

Claims, Numbers

1-31 as originally filed

Drawings, Sheets

1/6-6/6 as originally filed

2. With regard to the **language**, all the elements marked above were available or furnished to this Authority in the language in which the international application was filed, unless otherwise indicated under this item.

These elements were available or furnished to this Authority in the following language: , which is:

- ☐ the language of a translation furnished for the purposes of the international search (under Rule 23.1(b)).
☐ the language of publication of the international application (under Rule 48.3(b)).
☐ the language of a translation furnished for the purposes of international preliminary examination (under Rule 55.2 and/or 55.3).

3. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international preliminary examination was carried out on the basis of the sequence listing:

- ☐ contained in the international application in written form.
☐ filed together with the international application in computer readable form.
☐ furnished subsequently to this Authority in written form.
☐ furnished subsequently to this Authority in computer readable form.
☐ The statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.
☐ The statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished.

4. The amendments have resulted in the cancellation of:

- ☐ the description, pages:
☐ the claims, Nos.:
☐ the drawings, sheets:

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5. ☐ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed (Rule 70.2(c)).

(Any replacement sheet containing such amendments must be referred to under item 1 and annexed to this report.)

6. Additional observations, if necessary:

III. Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

1. The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non-obvious), or to be industrially applicable have not been examined in respect of:

- ☐ the entire international application,
☒ claims Nos. 3, 8, 11, 16, 20, 25 (partly)

because:

- ☐ the said international application, or the said claims Nos. relate to the following subject matter which does not require an international preliminary examination (specify):
☒ the description, claims or drawings (*indicate particular elements below*) or said claims Nos. are so unclear that no meaningful opinion could be formed (*specify*):

see separate sheet

- ☒ the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion could be formed.

- ☐ no international search report has been established for the said claims Nos.

2. A meaningful international preliminary examination cannot be carried out due to the failure of the nucleotide and/or amino acid sequence listing to comply with the standard provided for in Annex C of the Administrative Instructions:

- ☐ the written form has not been furnished or does not comply with the Standard.
☐ the computer readable form has not been furnished or does not comply with the Standard.

V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes: Claims	3-7, 11-15, 20-24, 26-31
	No: Claims	1, 2, 8-10, 16-19, 25
Inventive step (IS)	Yes: Claims	-
	No: Claims	1-31
Industrial applicability (IA)	Yes: Claims	See separate sheet
	No: Claims	

2. Citations and explanations

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Re Item I

Basis of the opinion

The examination is being carried out on the **following application documents:**

Text for the Contracting States:

AL AT BE BG CH CY CZ DE DK EE ES FI FR GB GR HU IE IT LI LT LU LV MC MK NL PL PT RO SE SI
SK TR

Description, pages:

1-14 as originally filed

Claims, No.:

1-31 as originally filed

Drawings, sheets:

1/6-6/6 as originally filed

The application concerns C7-C15 17-esters of etonogestrel (3-keto-desogestrel), monotherapies with these esters (claims 1,2,9,10,18,19,26-31), and combined therapies with estrogens, for female subjects (claims 8,16,17,25) as well as with androgen esters, for male subjects (claims 3-7, 11-15, 20-24). The combination therapies are for HRT and contraception (both male and female); the monotherapy is directed towards various gynaecological disorders (endometriosis, menorrhagia, metrorrhagia, PMS, dysmenorrhea; claims 28,31), as well as to contraception and HRT.

Re Item III

Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

1. An International Search Report was drawn up for the present set of claims, as far as the subject matter included therein is sufficiently defined and supported by (further) claims and by examples, with due regard to the general idea underlying the application as provided by the description.

For subject matter of the present application excluded from the search on this basis, no opinion with regard to novelty and inventive step is included in this preliminary examination.

The following points 1.1 and 1.2 are a specification of the reasons for possible exclusion of part of the application's subject matter from search and thus from preliminary examination:

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- 1.1 Present claims 3, 8, 11, 16, 20 and 25 relate to compositions, uses and methods involving an extremely large number of possible compounds by use of the terms "androgen ester" and "estrogen".

Support within the meaning of Article 6 PCT and/or disclosure within the meaning of Article 5 PCT is to be found, however, for only a small proportion of the compounds claimed.

- 1.2 The relative term "long-acting" used in claims 1, 9, 11, 16, 18, 20, 26 and 29 has no well-recognised meaning and leaves the reader in doubt as to the meaning of the technical feature to which it refers, thereby rendering the definition of the subject-matter of said claims unclear (Article 6 PCT).

2. Claims 18-25 (as far as relating to HRT treatments) and 29-31 relate to subject-matter considered by this Authority to be covered by the provisions of Rule 67.1(iv) PCT. Consequently, no opinion will be formulated with respect to the industrial applicability of the subject-matter of these claims (Article 34(4)(a)(i) PCT).

It is to be noted that the present application in fact lacks of unity of invention under Rule 68.1 PCT in view of D1 and D2 (see below, Section V). Based on D1 and D2, the application seems to represent 3 different inventions.

Since searching the different listed inventions did not cause major additional searching effort, all three inventions were searched; i.e. all originally filed claims 1-31 were searched in as far as possible in view of point III.1 above.

As a gesture towards the applicant, no objection to lack of unity is raised in the International procedure. However, the objection may be raised in a subsequent regional / national procedure.

Re Item V

Reasoned statement with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

For the assessment of the present claims 9-31 on the question whether they are industrially applicable, no unified criteria exist in the PCT Contracting States. The patentability can also be dependent upon the formulation of the claims. The EPO, for example, does not recognize as industrially applicable the subject-matter of claims to

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the use of a compound in medical treatment, but may allow, however, claims to a known compound for first use in medical treatment and the use of such a compound for the manufacture of a medicament for a new medical treatment.

Reference is made to the following documents:

- D1: EP-A-0 737 477
- D2: WO-A-97 03709
- D3: WO-A-00 42942
- D4: WO-A-99 67271
- D5: WO-A-99 67270
- D6: WO-A-94 04157
- D7: DE-A-4 240 806

NOVELTY

3. The present application does not satisfy the criterion set forth in Article 33(2) PCT because the subject-matter of Claims 1, 2, 8-10, 16-19 and 25 lacks novelty in respect of D1 and D2 as defined in the regulations (Rule 64(1)-(3) PCT).
- 3.1 D1 discloses progestagens as contraceptive and HRT (page 2, lines 6-10; page 6, lines 38-39), optionally in combination with estradiol (ester) as an estrogen (page 2, lines 6-10 and 34-35). The progestagen is very preferably 3-ketodesogestrel or an ester thereof (claims 1, 19-21). C7 and C11 esters are explicitly mentioned as possible esters of 3-ketodesogestrel (page 2, lines 48-51).
- 3.1.a Although D1 certainly refers to 17-esters of 3-ketodesogestrel as being contraceptive progestagens in general (e.g. page 2, lines 6-7), mono therapies of these esters are envisaged as well as combinations with estradiol (page 2, lines 34-35). In case of a single active agent being used, the passage on page 2, lines 47-51 represents a *specific* disclosure of the C7 and C11 17-esters of 3-ketodesogestrel. Furthermore, the present claims being anticipated by this disclosure are in no way limited to non-percutaneous formulations.
Also, present claims 8, 16 and 25 combine with "an estrogen" in general. It is considered that this claim to a combination with a generally described class of actives is explicitly disclosed in D1, e.g. page 2, lines 7-10 and 47-48. Finally, before addressing issues of selection on the grounds of a higher effectiveness (pharmacological profile) and whether the state of the art documents teach away from the subject matter of the present claims,

objections to novelty as elaborated above have to be overcome first, e.g. by introducing appropriate amendments; without, however, extending the scope of the claims to subject matter not originally filed (Art. 34.2.b PCT).

Thus D1 anticipates the subject matter of present claims 1, 2, 8-10, 16-19 and 25.

- 3.2 D2 discloses HRT and contraceptives (claim 15) to be treated with C1-20 esters of 3-ketodesogestrel; especially C2-12; more especially C2-8 (claims 1-3). The C8 ester of 3-ketodesogestrel is therefore explicitly disclosed in D2. Thus D2 anticipates the subject matter of present claims 1, 2, 8-10, 16-19 and 25.

- 3.2.a Similar considerations to the ones detailed in 3.1.a above apply for D2.

INVENTIVE STEP

4. The present application does not meet the requirements of Article 33(1) PCT because the subject-matter of Claims 1-7, 9-15 and 18-24 does not involve an inventive step in the sense of Article 33(3) PCT in view of D3 and D1, D2, D4, D5. Furthermore, the subject-matter of Claims 1, 2, 8-10, 16-19 and 25-31 does not involve an inventive step in the sense of Article 33(3) PCT in view of D6 (illustrated by D7) and D2, D1.
- 4.1 D3 discloses male contraceptive compositions comprising an androgen and a progestin. The androgen is preferably a testosterone ester, especially e.g. testosterone undecanoate, enanthate or buciclate (claim 5). The progestin may be chosen among a list of progestins, including 3-ketodesogestrel. Both the androgen and the progestin may be used in the form of a derivative, e.g. an ester.
- 4.1.2 From D2, esters of 3-ketodesogestrel, e.g. C8 esters (claim 3) with improved functionality (page 2, paragraph 3) are known (likewise, from D1, the C7 and C11 esters are known).
From D4 and D5, improved androgens w.r.t. testosterone undecanoate resp. testosterone cycloalkyl esters are known, viz. MENT-undecanoate (D4) and MENT-buciclate (D5).
- 4.1.3 Thus, in seeking to provide improved combinations of androgen esters and progestins for male contraception, a skilled person would need no inventive effort to replace the progestin of D3 with e.g. C8 ester of 3-ketodesogestrel and the androgen ester of D3 with MENT-undecanoate or -buciclate, as claimed in present claims 1-4, 9-12 and 18-21.
- 4.1.4 Dependent claims 5-7, 13-15 and 22-24 do not appear to contain any additional features which, in combination with the features of any claim to which they refer, meet the requirements of the PCT with respect to novelty and/or

inventive step, since the subject matter of these claims seems to consist merely of matters of common practice (optimizing dosages) in the technical field concerned.

4.2 Furthermore, the subject-matter of Claims 1, 2, 8-10, 16-19 and 25-31 does not involve an inventive step in the sense of Article 33(3) PCT in view of D2, D6 (illustrated by D7) and D1.

4.2.1 D2 discloses C1-20, preferably C2-12, most preferably C2-C8 etonogestrel esters (page 1, paragraphs 1,2) as a selection of etonogestrel formulations with improved penetration rate in transdermal formulations. Such esters are said to present advantages over the etonogestrel formulations of D6 in that they have improved solubility (page 2, paragraphs 2-5). Their use is in HRT and/or contraception when combined with an estrogen (claim 15), or in contraception or treatments of endometriosis or PMS when applied as monotherapy (claim 14).

4.2.2 D6 discloses the use of etonogestrel as a contraceptive agent or in treatments of endometriosis and PMS (when used as monotherapy, claim 12); and as contraceptive agent or in treatments of HRT (when used in combination with an estrogen, claim 13). D7 illustrates the fact that etonogestrel esters are also envisaged for similar uses (claims 12,13 and claim 2).

D6 (and D7) also envisages the use of preferably C14 fatty acid esters as penetration enhancers in transdermal formulations of etonogestrel (examples 2,4); C12 fatty acid esters are also mentioned (page 3, paragraph 1).

4.2.3 The difference between the disclosures of D2, D6 (as illustrated by D7) and the present application resides in the choice of the length of the fatty acid residue in the 17-ester of etonogestrel.

The objective problem can therefore be formulated as: providing improved (transdermal) formulations of etonogestrel esters.

4.2.4 D1 suggests the use of 17-esters, specifically indicating C7 and C11 esters, of etonogestrel in percutaneous formulations. C8 and C12 esters were explicitly disclosed in D2 to solve the same technical problem, although preference in D2 goes to the shorter chain fatty acids (C2-C8). D6 and D7 indicate the use of e.g. C2, C6, C16, C18, C12 and especially C14 fatty acid esters (although not 17-esters of etonogestrel) as penetration enhancers in transdermal formulations of etonogestrel.

- 4.2.5 Therefore, in the absence of an indication in the present application as to how the selection of C10-C12 esters of etonogestrel would give rise to a technical effect unexpected from the prior art (D2, D6, illustrated by D7, D1), present claims 1, 2, 8-10, 16-19 and 25-31 are considered to lack an inventive step.

FURTHER OBJECTIONS

Contrary to the requirements of Rule 5.1(a)(ii) PCT, the relevant background art disclosed in D1-D6 is not mentioned in the description, nor are these documents identified therein.